

Tenomodulin, serum amyloid A and the serum amyloid A receptor selenoprotein S – implications for metabolic disease



GÖTEBORGS UNIVERSITET

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs Universitet kommer att offentligen försvaras i sal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg, torsdagen den 27:e maj kl 09:00

av

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Avhandlingen baseras på följande delarbeten:

- I. Tenomodulin is highly expressed in adipose tissue, increased in obesity, and down-regulated during diet-induced weight loss.**
Saiki A*, Olsson M*, Jernås M, Gummesson A, McTernan PG, Andersson J, Jacobson P, Sjöholm K, Olsson B, Yamamura S, Walley A, Froguel P, Carlsson B, Sjöström L, Svensson P-A, Carlsson LMS.
J Clin Endocrinol Metab. 2009;94(10):3987-94.
*These authors contributed equally.
- II. Association of serum amyloid A levels with adipocyte size and serum levels of adipokines: differences between men and women.**
Sjöholm K, Lundgren M, Olsson M, Eriksson JW.
Cytokine. 2009;48(3):260-6
- III. Expression of the Selenoprotein S (SELS) gene in subcutaneous adipose tissue and SELS genotype are associated with metabolic risk factors.**
Olsson M, Olsson B, Jacobson P, Thelle DS, Björkegren J, Walley A, Froguel P, Carlsson LMS, Sjöholm K.
Submitted manuscript
- IV. Establishment of a transgenic mouse model specifically expressing human serum amyloid A in adipose tissue.**
Olsson M, Ahlin S, Olsson B, Svensson P-A, Ståhlman M, Borén J, Carlsson LMS, Sjöholm K.
Manuscript

Tenomodulin, serum amyloid A and the serum amyloid A receptor selenoprotein S – implications for metabolic disease

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Abstract

Obesity and obesity-related metabolic diseases are associated with a low-grade inflammation, including slightly increased serum levels of the acute phase protein serum amyloid A (A-SAA). A-SAA is one amongst several adipose tissue (AT) produced proteins suggested to influence development of metabolic diseases. The A-SAA protein may have pro-atherogenic functions, and release of A-SAA from the AT may contribute to the development of cardiovascular disease. Furthermore, A-SAA is functionally linked to insulin resistance via one of its receptors, selenoprotein S (SELS). The tenomodulin (TNMD) gene is expressed in adipose tissue, but its role in obesity is unclear. The overall aim of this thesis was to increase our understanding of how TNMD, A-SAA and SELS relate to obesity and obesity-associated metabolic diseases. An additional aim was to establish a mouse model mirroring the human A-SAA production in AT.

To achieve these goals, we (1) investigated TNMD gene expression in human AT by DNA microarray and real-time PCR analysis; (2) analyzed serum levels of A-SAA in a cohort with a wide range in body mass index and metabolic parameters; (3) analyzed SELS gene expression and genotyped three SELS polymorphisms, previously associated with serum levels of inflammatory markers, in a case-control study of coronary heart disease and (4) generated a mouse model with transgenic over-expression of the human SAA1 (hSAA) gene in AT.

The TNMD gene was highly expressed in human AT, with a higher expression in obese compared to lean subjects. Furthermore, TNMD gene expression was down-regulated during diet-induced weight loss. These data suggest that TNMD plays a role in the adipose tissue.

Inflammatory markers and measures of glycemic control were strongly associated with serum levels of A-SAA. The strongest associations were found in women, and serum levels of A-SAA were associated with adipocyte size in women only. These data suggest that sex-specific factors have to be considered when analyzing serum levels of A-SAA in relation to metabolic disease.

Gene expression of SELS in AT was associated with measures of obesity. Furthermore, genetic variants in the SELS gene were associated with serum levels of glucose, measures of insulin resistance and blood pressure. These findings suggest that SELS plays a role in the development of metabolic disease.

In the hSAA mouse model, hSAA was specifically expressed in AT and plasma levels of hSAA were increased in obese mice. The hSAA protein was found to be co-localized to high-density lipoprotein containing fractions of plasma.

In conclusion, the results of this thesis suggest that TNMD, A-SAA and SELS have metabolic effects that should be further explored. The established hSAA transgenic mouse model opens the possibility to further explore the effects of AT-derived A-SAA on cardiovascular disease.